Practical Glutathione Measurement in Human Brain at 3 T

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Introduction: Glutathione (GSH) is a primary antioxidant and detoxifier in human body. In vivo measurement of GSH concentration in human brain may play a role in diagnosing and treating diseases such as cancer, AIDS, Parkinson's disease, and stroke. A J-difference editing pulse sequence MEGA-PRESS [1] has been used to measure GSH in human brain with a 4 T magnet and a surface ^{1}H quadrature transceiver [2]. The pulse sequence had a TR of 4.5 s, a TE of 68 ms, and 256 or 512 acquisitions. We implemented a MEGA-PRESS pulse sequence with rearranged crusher gradients on a 3 T Philips scanner with a standard T/R volume head coil. From phantom and in vivo experiments, we found that a longer TE of 131 ms resulted in good GSH signal, smaller water baseline, as well as near in-phase GSH and co-edited NAA resonances. Our pulse sequence had a TR of 2 s, a TE of 131 ms, and 256 acquisitions, thus a total scan time of 9 minutes. A novel spectral registration method [3] was also developed to perform frequency, phase, and linear baseline corrections automatically.

Method and Results: The MEGA-PRESS pulse sequence consists of two types of acquisitions: an "on" acquisition in which the selective inversion pulses are tuned at the resonance frequency of cysteinyl α proton at 4.56 ppm [4] to partially refocus the J-evolution of the GSH resonances of interest at 2.95 ppm (cysteinyl β protons), and an "off" acquisition in which the frequency of the selective inversion pulses is shifted to a higher value to allow the J-evolution of the GSH resonances at 2.95 ppm to fully develop. The difference between an "on" spectrum and an "off" spectrum cancels out major NAA, creatine, and choline singlet peaks. The GSH resonances at 2.95 ppm stand out along with the co-edited NAA/NAAG resonances.

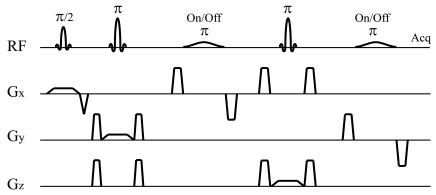

Fig. 1. *MEGA-PRESS pulse sequence with rearranged crusher gradients*

A MEGA-PRESS pulse sequence with rearranged crusher gradients (Fig. 1) was implemented on a 3 T Philips Achieva scanner. A standard 30 cm diameter T/R volume head coil was used to perform the experiments. The re-arrangement of the crusher gradients reduces signal decay due to subject motion for scans with a relatively long TE. Using this pulse sequence, a GSH phantom with 20 mM GSH concentration was scanned seven times with different TE values incrementing from 80 ms to 140 ms (Fig. 2). A volume of interest (VOI) of $3\times3\times3$ cm^3 in the center of the phantom was selected. The selective inversion pulses were Gaussian shaped pulses with 15.5 ms duration and 80 Hz bandwidth at half-height. The time delay between the excitation pulse and the first refocus pulse was 8.5 ms. Shimming and receiver gain for all scans kept the same. In post-processing, 2 Hz Lorenzian line broadening was applied to the spectra. Fig. 2 shows that the J-difference spectra with longer TE values have greater GSH peak amplitudes and areas. This result is different from that of the GSH phantom experiment at 4 T, in which a shorter TE value results in greater GSH peak amplitude [5]. One reason for this difference might be due to different field strengths. Differences in the timing of the RF pulses can also cause the GSH peak vary differently when TE changes.

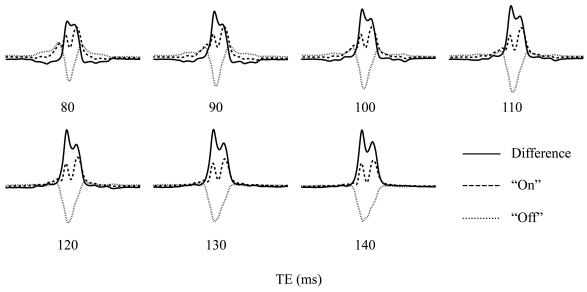

Fig. 2. *GSH phantom experiment with different TE values*

From analyzing the results of phantom and in vivo experiments, we chose 131 ms as our optimal TE for in vivo scans. A TE of 131 ms gives near maximum GSH peak amplitude and area. More importantly, a TE of 131 ms results in a much smaller water baseline compared to a shorter TE such as 68 ms. In addition, the GSH and co-edited NAA resonances are approximately in-phase at TE of 131, which is preferable in quantification.

Due to subject motion and system instabilities, spectrum from each acquisition changes in water baseline, frequency, and phase. To measure a small GSH signal, it becomes necessary to correct for these errors for each acquisition. Residual water baseline is a bigger problem for GSH measurement than other J-difference editing experiments such as GABA measurement because the frequency of the selective inversion pulses is very close to the resonance frequency of water. We developed a fully automated and adaptive spectral registration method to perform frequency, phase, and linear baseline corrections simultaneously.

Over forty scans from ten normal volunteers and four stroke patients have been performed in accordance with procedures approved by our institutional review board. GSH peak can be observed from all scans. We used a head set and foam pads to constrain head movement of the subject. Our spectral registration method appears to be robust to correct for errors caused by small motions of the head. The same pulse sequence was used for scanning both normal volunteers and stroke patients. The pulse sequence had a TR of 2 s, a TE of 131 ms, a pair of Gaussian shaped inversion pulses with 28 ms duration and 55 Hz bandwidth at half-height, and a 13.4 ms time delay between the excitation pulse and the first refocus pulse. We used two VOI sizes for normal volunteers, which were $5\times3\times3$ cm^3 and $3\times3\times3$ cm^3. For the VOI of $5\times3\times3$ cm^3, second order pencil beam shimming was performed on the VOI. For the VOI of $3\times3\times3$ cm^3, second order pencil beam shimming was performed on a larger volume that encompassed the VOI. For scanning stroke patients, a VOI of $5\times3\times3$ cm^3 was used for all scans. Fig. 3 shows the J-difference spectrum of a normal volunteer. The VOI was located in the parietal lobe. Fig. 4 shows two J-difference spectra of a stroke patient, one from the lesion side and the other from the contralateral side.

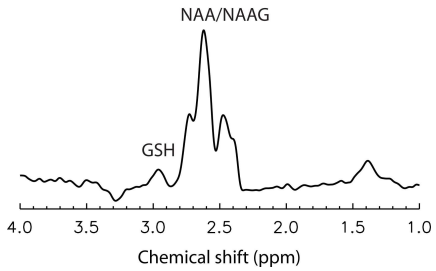

Fig. 3. *J-difference spectrum of a normal volunteer with a VOI of $3\times3\times3$ cm^3.*

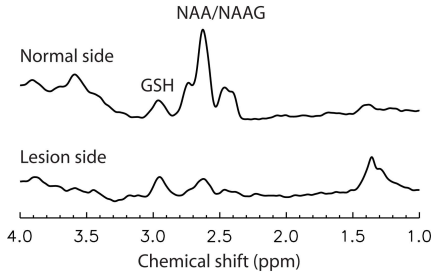

Fig. 4. *J-difference spectra of a stroke patient with a VOI of $5\times3\times3$ cm^3. .*

Conclusion and Future work: This work demonstrates the ability to consistently measure GSH in human brain on a commercial 3 T scanner with a scan time of nine minutes. A relatively long TE of 131 ms yields good GSH signal, smaller water baseline, as well as near in-phase GSH and co-edited NAA/NAAG resonances. The spectral registration method can perform frequency, phase, and linear baseline corrections without human intervention. From scanning normal volunteers and stroke patients, this work appears to be a step forward toward practical use of GSH measurement in clinical studies. Efforts will be undertaken to quantify GSH concentration in vivo.

References: 1. Mescher M, et. al., NMR Biomed 11:266-272 (1998) 2. Terpstra M, et. al., MRM 50:19-23 2003)
3. An L, et. al., ISMRM 2008, submitted. 4. Trabesinger AH, et. al., MRM 42:283-289 (1999)
5. Terpstra M, et. al., MRM 56:1192-1199 (2006)